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(PCT Rule 61.2)

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Date of mailing (day/month/year) 20 April 2000 (20.04.00)	
International application No. PCT/US99/16031	Applicant's or agent's file reference X-12383M
International filing date (day/month/year) 15 July 1999 (15.07.99)	Priority date (day/month/year) 23 July 1998 (23.07.98)
Applicant HOFFMANN, James, Arthur et al	

1. The designated Office is hereby notified of its election made:

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22 February 2000 (22.02.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US99/16031
A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00, 38/24

US CL :514/8, 12; 530/397, 398, 399

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/8, 12; 530/395, 397, 398, 399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,767,067 A (ARPAIA et al) 16 June 1998, col. 10, example 3 and claims 4-10.	1-61
A	FURUHASHI, M. et al. Fusing the Carboxy-Terminal Peptide of the Chorionic Gonadotropin (CG) beta-Subunit to the Common alpha-Subunit: Retention of O-linked Glycosylation and Enhanced in Vivo Bioactivity of Chimeric Human CG. Molecular Endocrinology. 1995, Vol. 9, No. 1, pages 54-63.	1-61
X - Y	US 5,733,572 A (UNGER et al) 31 March 1998, col. 22, line 3; col. 19, line 4; col. 26, line 55 to col. 27, line 13; claims 1, 4 and 8.	1, 4, 8 ----- 2-3, 5-7, 9-61

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 SEPTEMBER 1999

Date of mailing of the international search report

14 OCT 1999

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INTERNATIONAL SEARCH REPORT

International application No. — —

PCT/US99/16031

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS; STN; CAPLUS, Medline, Embase, Biosis

search terms: follicle stimulating hormone, FSH, variant, alpha subunit, beta subunit, infertility, preservative, phenol, phosphate buffer, isotonic, kit,

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We claim:

1. A formulation comprising FSH or a FSH
5 variant, containing an alpha and beta subunit, and a
preservative selected from the group consisting of phenol,
m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol,
alkylparaben (methyl, ethyl, propyl, butyl and the like),
10 benzalkonium chloride, benzethonium chloride, sodium
dehydroacetate and thimerosal, or mixtures thereof in an
aqueous diluent.
2. A formulation of Claim 1, wherein the
preservative is phenol, m-cresol, chlorocresol, or a mixture
thereof.
- 15 3. A formulation of Claim 2, wherein the
concentration of FSH or a FSH variant is about 1.0 µg/ml to
about 50 mg/ml.
4. A formulation of Claim 3, further comprising
an isotonicity agent.
- 20 5. A formulation of Claim 4, further comprising
a physiologically acceptable buffer.
6. A formulation comprising FSH or a FSH variant
lyophilized in a first vial, and a second vial containing a
preservative selected from the group consisting of phenol,
25 m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol,
alkylparaben (methyl, ethyl, propyl, butyl and the like),
benzalkonium chloride, benzethonium chloride, sodium
dehydroacetate and thimerosal, or mixtures thereof in an
aqueous diluent.
- 30 7. A formulation of Claim 1, wherein said FSH or
a FSH variant and preservative are in solution.
8. A formulation of Claim 1, wherein said FSH or
a FSH variant is at least one compound selected from the
group consisting of:
35 (a): α-subunit:(SEQ ID NO:1)

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FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
5 VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α -subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β -subunit: (SEQ ID NO:4)

10 NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNDSSTDCTVRGLGPSYCSFGDMKE

(c): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

15 β -subunit: (SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d): α -subunit: (SEQ ID NO:7)

20 FPDGEFTMQGCPECKLKENKYFSKLGAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:8)

NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit: (SEQ ID NO:9)

25 FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:10)

RSCELTNITITVEKEECSCFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDRDSTDCTVRGLGPSYCSFSDIRE

30 (f): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:11)

35 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

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(g): α -subunit:(SEQ ID NO:5)APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS β -subunit:(SEQ ID NO:12)5 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM(h): α -subunit:(SEQ ID NO:5)APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS10 β -subunit:(SEQ ID NO:13)NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

15 9. A method of treating infertility which
comprises administering to a patient in need thereof a
formulation according to Claim 1.

10. A method of Claim 9, wherein said
patient is selected from the group consisting of a human,
sheep, cow, pig, horse, or rabbit.

20 11. A process for preparing a preserved
solution formulation of FSH or a FSH variant, containing an
alpha and beta subunit, which comprises admixing said FSH or
a FSH variant and a preservative selected from the group
consisting of phenol, m-cresol, p-cresol, o-cresol,
25 chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl,
propyl, butyl and the like), benzalkonium chloride,
benzethonium chloride, sodium dehydroacetate and thimerosal,
or mixtures thereof, in an aqueous diluent.

30 12. An article of manufacture for human
pharmaceutical use, comprising packaging material and a vial
comprising a solution of FSH or a FSH variant, containing an
alpha and beta subunit, and a preservative solution, wherein
said packaging material comprises a label which indicates
that said solution may be held over a period of 24 hours or
35 greater.

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13. The article of manufacture of Claim 12, wherein said vial is a glass container having a stopper for multi-use administration.

14. The article of manufacture of Claim 12, wherein said vial is a blister pack, capable of being punctured and used in pulmonary administration.

15. The article of manufacture of Claim 12, wherein said vial is a pen-injector device.

16. An article of manufacture, comprising packaging material, a first vial comprising lyophilized FSH or a FSH variant, containing an alpha and beta subunit, and a second vial comprising a preservative solution, wherein said packaging material comprises a label which instructs a patient to reconstitute the said lyophilized FSH or a FSH variant in the preservative solution for use over a period of of 24 hours or greater.

17. The article of manufacture of Claim 16, wherein said first vial and said second vial are embodied in a pen-injector device.

18. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, in an preserved solution, said solution being suitable for administration over a period of 24 hours or greater.

19. A method of using a stable solution of FSH or a FSH variant, containing an alpha and beta subunit to treat infertility in a patient, which comprises administering to a patient in need thereof a solution of FSH or a FSH variant in a stable solution, said solution being suitable for administration over a period of 24 hours or greater.

20. The use of at least one alpha or beta polypeptide of a FSH or a FSH variant in the preparation of a preserved formulation adapted for administration over a period of 24 hours or greater.

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21. A stable formulation comprising at least one FSH or a FSH variant, containing an alpha and beta subunit, and phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

22. A formulation of Claim 21, wherein the concentration of said FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

23. A formulation of Claim 21, further comprising an isotonicity agent.

24. A formulation of Claim 21, wherein said buffer is phosphate buffered saline.

25. A formulation comprising a first vial containing a lyophilized FSH or a FSH variant containing an alpha and beta subunit, and a second vial containing phosphate buffer containing saline or a salt.

26. A formulation of Claim 21, wherein said FSH or a FSH variant and said phosphate buffer are in solution.

27. A formulation of Claim 21, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit: (SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α-subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTMLVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit: (SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNSTDCTVRGLGPSYCSFGDMKE

(c): α-subunit: (SEQ ID NO:5)

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APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:6)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
5 VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE

(d): α -subunit: (SEQ ID NO:7)

FPDGFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS

β -subunit: (SEQ ID NO:8)

10 NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTYPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE

(e): α -subunit: (SEQ ID NO:9)

FPDGFTMQGCPECKLKENKYFSKPDAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

15 β -subunit: (SEQ ID NO:10)

RSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKE
LVYETVKVPGCAHHADSLYTYPVATECHCGKCDSDSTDCTVRGLGPSYCSFSDIR
E

(f): α -subunit: (SEQ ID NO:5)

20 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

25 (g): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:12)

30 NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α -subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS

β -subunit: (SEQ ID NO:13)

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NSCEL TNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

28. A method of treating infertility which
5 comprises administering to a patient in need thereof a
formulation according to Claim 21.

29. A method of Claim 28, wherein said
patient is selected from the group consisting of a human,
sheep, cow, pig, horse, or rabbit.

10 30. A process for preparing a stable solution
formulation of FSH or a FSH variant, containing an alpha and
beta subunit, which comprises admixing a FSH or a FSH
variant in phosphate buffer containing saline or a salt.

31. An article of manufacture for pharmaceutical
15 use, comprising packaging material and a vial comprising a
stable solution of FSH or a FSH variant, containing an alpha
and beta subunit, in an aqueous diluent, wherein said
packaging material comprises a label which indicates that
such solution is suitable for use over a period of 24 hours
20 or greater.

32. The article of manufacture of Claim 31,
wherein said vial is a glass container having a stopper for
multi-use administration.

33. The article of manufacture of Claim 31,
25 wherein said vial is a blister pack, capable of being
punctured and used in pulmonary administration.

34. The article of manufacture of Claim 31,
wherein said vial is a pen-injector device.

35 30 An article of manufacture, comprising
packaging material, a first vial comprising a lyophilized
FSH or a FSH variant containing, an alpha and beta subunit,
and a second vial comprising a stable aqueous diluent,
wherein said packaging material comprises a label which
instructs a patient to reconstitute said FSH or a FSH
35 variant in the aqueous diluent to form a solution that is
suitable for use over a period of 24 hours or greater.

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36. The article of manufacture of Claim 35, wherein said first vial and said second vial are embodied in a pen-injector device.

37. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, in an aqueous phosphate buffered diluent, said solution being suitable for administration over a period of 24 hours or greater.

38. A method of using a solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient, which comprises administering to a patient in need thereof a stable solution of FSH or a FSH variant in an aqueous diluent suitable for use over a period of 24 hours or greater.

39. The use of at least one polypeptide of a FSH or a FSH variant in the preparation of a stable formulation adapted for administration over a period of 24 hours or greater.

40. A formulation as described herein.

41. An article of manufacture as described herein

42. A process as described herein.

43. A use as described herein.

44. A method as described herein.

45. Use of a formulation of claim 1 for treating infertility in a patient in need thereof.

46. Use of a formulation of claim 1 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

47. Use of a preserved solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, said solution being suitable for administration over a period of 24 hours or greater.

48. Use of a stable solution of FSH or a FSH variant, containing an alpha and beta subunit, to treat

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infertility in a patient, which comprises administering to a patient in need thereof a solution of said FSH or a FSH variant in a phosphate buffer, containing saline or a salt, over a period of 24 hours or greater.

5 49. Use of a formulation of Claim 21 for treating infertility in a patient in need thereof.

 50. A use of Claim 49 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

10 51. Use of stable stable solution of purified FSH or a FSH variant, containing an alpha and beta subunit, in a phosphate buffer containing saline or a salt suitable for administration over a period of 24 hours or greater for treating infertility in a patient in need thereof.

15 52. Use of a stable solution FSH or a FSH variant, containing an alpha and beta subunit, to treat infertility in a patient in need thereof, wherein said stable solution of said FSH or a FSH variant in phosphate buffer containing saline or a salt is suitable for use over
20 a period of 24 hours or greater.

 53. A process of producing a formulation comprising admixing FSH or a FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol,
25 chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

 54. A process of producing a stable formulation
30 comprising admixing at least one FSH or a FSH variant, containing an alpha and beta subunit, and a phosphate buffer containing saline or a salt, wherein said FSH or a FSH variant comprises at least 90% FSH or a FSH variant dimers after 60 days at 23°C.

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55. A process of Claim 53, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

56. A process according to any of Claims 53-54, wherein the concentration of FSH or a FSH variant is about 1.0 µg/ml to about 50 mg/ml.

57. A process according to any of Claims 53-54, further admixing an isotonicity agent.

58. A process of Claim 53-54, further admixing a physiologically acceptable buffer.

59. A process comprising preparing a FSH or a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

60. A process of Claim 59, wherein said FSH or a FSH variant and preservative are further put into solution.

61. A process according to any of claims 53-54, wherein said FSH or a FSH variant is at least one compound selected from the group consisting of:

(a): α-subunit: (SEQ ID NO:1)

FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTM LVPKN
ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS

β-subunit: (SEQ ID NO:2)

RSCELTNITITVEKEECGFCISINTTWCAGYCYTRDLVYRDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCSKCDSDSTDCTVRGLGPSYCSFREIKE

(b): α-subunit: (SEQ ID NO:3)

FPDGEFTTQDCPECKLRENKYFFKLGVPYQCKGCCFSRAYPTPARSRKTM LVPKN
ITSESTCCVAKAFIRVTVMGNIKLENHTQCYCSTCYHHKI

β-subunit: (SEQ ID NO:4)

NSCELTNITIAVEKEGCGFCITINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATACHCGKCNSDSTDCTVRGLGPSYCSFGDMKE

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(c): α -subunit: (SEQ ID NO:5)APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS β -subunit: (SEQ ID NO:6)5 NSCELTNITIAIEKEEFCRISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMKE(d): α -subunit: (SEQ ID NO:7)FPDGEFTMQGCPECKLKENKYFSKLGAPIYQCMGCCFSRAYPTPARSKKTMLVPKN
ITSEATCCVAKAFTKATVMGNARVENHTECHCSTCYHKS10 β -subunit: (SEQ ID NO:8)NSCELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKTCTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSEMKE(e): α -subunit: (SEQ ID NO:9)FPDGEFTMQGCPECKLKENKYFSKPDAPYQCMGCCFSRAYPTPARSKKTMLVPKN
15 ITSEATCCVAKAFTKATVMGNVRVENHTECHCSTCYHKS β -subunit: (SEQ ID NO:10)RSELTNITITVEKEECNFCISINTTWCAGYCYTRDLVYKDPARPNIQKACTFKEL
VYETVKVPGCAHHADSLYTPVATECHCGKCDSDSTDCTVRGLGPSYCSFSDIRE(f): α -subunit: (SEQ ID NO:5)20 APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS β -subunit: (SEQ ID NO:11)NSCELTNITIAIEKEEFCRISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE25 (g): α -subunit: (SEQ ID NO:5)APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS β -subunit: (SEQ ID NO:12)30 NSCELTNITIAIEKEEFCRISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM(h): α -subunit: (SEQ ID NO:5)APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYHKS β -subunit: (SEQ ID NO:13)

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NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSSTDCTVRGLGPSYCSFGEMK

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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		